PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/050272	21.01.2005	23.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07C233/36, C07C233/78, C07C311/05, C07D471/10, C07D211/14, C07D211/76, C07D207/26, C07D239/10,

Applicant
SPEEDEL EXPERIMENTA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/050272

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/050272

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-5,7,8
	No:	Claims	1,6
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations

see separate sheet

10/586814
IAP11 Rec'd PCT/PTO 24 JUL 2006

D1: WO 03/050073 A (ELAN PHARMACEUTICALS, INC; PHARMACIA & UPJOHN COMPANY; TENBRINK, RUTH;) 19 June 2003 (2003-06-19)

D2: WOOD J M ET AL: "Structure-based design of aliskiren, a novel orally effective renin inhibitor" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 308, no. 4, 5 September 2003 (2003-09-05), pages 698-705, XP004447169 ISSN: 0006-291X

D3: EP-A-0 468 641 (SHIONOGI SEIYAKU KABUSHIKI KAISHA TRADING UNDER THE NAME OF SHIONOGI &) 29 January 1992 (1992-01-29)

D4: ALLIKMETS K: "ALISKIREN SPEEDEL" CURRENT OPINION IN INVESTIGATIONAL DRUGS, PHARMAPRESS, US, vol. 3, no. 10, 2002, pages 1479-1482, XP009017210 ISSN: 1472-4472

D5: RADDATZ P ET AL: "RENIN INHIBITORS CONTAINING NEW P1-P1' DIPEPTIDE MIMETICS WITH HETEROCYCLES IN P1'" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 19, 18 September 1992 (1992-09-18), pages 3525-3536, XP002050635 ISSN: 0022-2623

1. Novelty

D1 discloses the compound N-[(1S)-1-((1R)-2-{[1-(3-bromophenyl) cyclopropyl] amino} hydroxyethyl) -3-methyl-4-phenylbutyl] acetamide hydrochloride (p.231, ex.8) which falls within the scope of formula (I) of claim 1. Used as anti-Alzheimer agent. The subject-mater of claims 1 and 6 is not novel over D1.

2. Inventive step

2.1 The closest prior art D2 discloses aliskiren and derivatives as renin inhibitors and structurally differs from the presently claimed compounds by the fact that a 1-amido, 3-hydroxy,4-amino phenylheptane chain is present in the compounds of D1 while the application discloses 1-amino, 2-hydroxy,3-amino-hexane chain. In other words D2 lacks the hydroxyethylene diamine linker.

A skilled person wishing to develop alternative renin inhibitors to the aliskiren derivatives would have looked at structure of compounds having similar use like the

ones disclosed in documents D3-D5. These documents disclose dipeptides renin inhibitors (see search report) which possess a N-CHR-CHOH-CH2-N< linker like in the presently claimed compounds and differ by the fact that the phenylpropyl moity of the present compounds is replaced by a cyclohexylmethyl group in the dipeptides of D3 D5.
The fact that the molecules of D3/D5 possess also a renin inhibitor activity strongly encourages a skilled person whishing to develop alternative renin inhibitors to graft one part of the renin inhibitor of D2 to a part of another renin inhibitors like the ones of D3/D5.

2.2 Furthermore, since the applicant has not provided any biological tests (apart from a vague sentence on page 8 stating that the compounds exhibit inhibiting action in vitro), it is at present impossible to know if the technical problem has been properly solved on the whole scope of claim 1, which leads to a lack of inventive step.

2.3 For these reasons, the subject-matter of claims 1-8 is not inventive.